



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(54) Title:</b> TREATMENT OF ALLERGIC CONDITIONS  <b>(57) Abstract</b>  Orally administered sodium cromoglycate has been found to be effective in the treatment of allergic conditions such as asthma, general food allergies, ulcerative colitis, atopic eczema, chronic urticaria and irritable bowel syndrome if it is presented as individually enteric-coated microgranules or microgranules packaged in an enteric-coated capsule and/or if the patients are first selected to have a total serum IgE level of at least 150 iu/ml.		

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## TREATMENT OF ALLERGIC CONDITIONS

The present invention relates to the treatment of allergic conditions, in particular allergic conditions which relate to the nature of the food or drink consumed by the patient. Allergy to ingested substances can manifest itself in a wide range of symptoms affecting any organ in the body. Commonly it affects particularly the gastrointestinal tract, the skin, the lung, the nose and the central nervous system. Allergic reactions to ingested substances affecting these organs can manifest themselves as abdominal pain, abdominal bloating, disturbance of bowel function, vomiting, rashes, skin irritation, wheezing and shortness of breath, nasal running and nasal blockage, headache and behavioural changes. In addition in severe food allergic reactions, the cardiovascular and respiratory systems can be compromised giving anaphylactic shock and in some cases death.

It is also recognised that in certain chronic diseases, allergy to ingested substances is the probable cause of the disease in a proportion of patients. These diseases include anaphylactic shock, atopic dermatitis, chronic urticaria, asthma, allergic rhinitis, irritable bowel syndrome, migraine and hyperactivity in children. It is also possible that food allergy may be a factor in certain patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease).

This vast array of symptoms and diseases presents the medical practitioner with tremendous problems of diagnosis and management. In the absence of any reliable tests for food allergy other than double-blind, placebo-controlled, food challenges which are time-consuming,

expensive and potentially dangerous, many practitioners are often reluctant to regard allergy as the cause, and rely on symptomatic treatment for management. For example, wheezing and asthma are treated with bronchodilators, atopic dermatitis with topical  
5 corticosteroids, rhinitis with nasal decongestants and irritable bowel syndrome with anti-spasmodics.

One drug which has been investigated over the years for treating allergic conditions, particularly asthma, is sodium cromoglycate. This was  
10 initially launched in the 1960's by Fisons as an inhaled prophylactic treatment for asthma. In 1972, an insufflated powder formulation "Rynacrom" was introduced for nasal allergies, followed in 1975 by a more convenient nasal spray solution. In 1976, a dropper bottle solution called "Opticrom" was launched for eye allergies and, in 1978, an oral  
15 powder ("Nalcrom") was marketed initially for the treatment of inflammatory bowel disease and later for food allergy. However, various clinical studies have failed to confirm that the oral formulation of sodium cromoglycate is adequately effective in inflammatory bowel disease and this indication was withdrawn in the early 1980's.

20

The clinical efficacy of oral sodium cromoglycate (Nalcrom) has been reported as being variable with some authorities reporting good effects and others variable or poor effects.

25 We have now investigated the matter more closely and we have found that chromones such as sodium cromoglycate are effective in treating these various allergic conditions providing that they are formulated in a

particular manner and/or provided that the patient is first selected according to a specific criterion.

A first aspect of the invention provides an oral drug delivery composition comprising a chromone, characterised in that the chromone is made bioavailable in the small intestine following human oral administration. Preferably a composition wherein the composition comprises microgranules of up to 1.5 mm diameter, each microgranule having an enteric coating.

10

The chromone is preferably sodium cromoglycate or nedocromil sodium.

References to sodium cromoglycate hereafter refer to the class of chromones as well as to the individual compound.

15 The current "Nalcrom" formulation of sodium cromoglycate consists of a powder which is either taken by the patient as a solution (ie after dissolving the powder in water) or presented in a gelatin capsule which dissolves in the stomach. As one would expect, the various Fisons patent specifications concerning sodium cromoglycate list a vast number  
20 of theoretical formulations of the drug, practically none of which have been put into effect. Thus, GB 1 423 985 discloses an enteric coated composition intended to make the drug available "at an appropriate part of the gastro-intestinal tract" (unspecified) and GB 1 549 229 discloses a gelatin capsule containing granules of the drug, for oral use in the  
25 treatment of allergic conditions. Both of these two patent documents date from the 1970's and it appears not to have been obvious to have actually made these compositions in practice. Moreover, there has been no prior disclosure of the composition of the present invention, in which

fine particles containing the drug are individually coated with an enteric coating.

The previously proposed gelatin capsules of sodium cromoglycate are, we believe, of low bioavailability because the sodium salt of the drug is converted in the acidic conditions of the stomach into insoluble and inactive cromoglycic acid. Although, in the alkaline medium of the duodenum, the cromoglycic acid will convert back to a salt, this is unlikely to be the sodium salt and is more likely to be an insoluble and inactive salt such as a calcium salt. The enteric-coated formulations which have been proposed previously, at least on paper, similarly may be of low bioavailability because the sodium cromoglycate is released into the duodenum in a lump, rather than being dispersed evenly throughout the food material passing through the small intestine. We consider it to be desirable for the drug to be applied evenly and consistently across the whole surface area of the mucosa in the small intestine prior to and at the same time as the intestine is exposed to the food which is causing the allergy.

Thus a second aspect of the invention is a composition as in the first aspect of the invention, wherein the composition comprises microgranules of up to 1.5 mm diameter which are packaged in a hard or soft capsule, which capsule has an enteric coating. Thus, microgranules may be produced as described in Example 1 and put into a gelatin capsule (for example, a capsule which consists essentially of gelatin) which is then enteric coated, for example as described below. Suitable capsules are well known to those skilled in the art. The capsules should not be such that they may pass through the small

intestine or even the whole gastrointestinal tract substantially intact. The capsules may be such that if they were used without the enteric coating they may release their contents in the stomach. It is preferred that the capsules and enteric coating are chosen such that maximum  
5 disintegration of the coated capsules occurs within the small intestine (duodenum, jejunum, ileum). Preferably, drug is made bioavailable from the duodenum onwards. Suitable coatings which may be used in the capsules of the invention are discussed below. It will be appreciated that the microgranules may, but do not necessarily, each have an enteric  
10 coating. It is preferred in this embodiment that each microgranule does not have an enteric coating.

Preferably, the microgranules in the formulation of the present invention have a size of 25-250  $\mu\text{m}$ , 25 to 500  $\mu\text{m}$  or 200 to 1100 $\mu\text{m}$ .  
15 Microgranules at the smaller end of these ranges (about 25 to 250  $\mu\text{m}$ ) may be classed as granules, whereas microgranules at the larger end of the ranges (for example, about 200 to 1100  $\mu\text{m}$ ) may be referred to as pellets (which may be melt or wet-formed, as described below).

20 It is particularly beneficial if differing groups or populations of the individual microgranules/pellets have differing enteric coatings such that the drug content of the microgranules/pellets is made bioavailable at differing locations in the small intestine. A drug can be made "bioavailable", for example, either as a result of the coating  
25 disintegrating or as a result of the coating becoming porous. Preferably, at least 25%, 50%, 75% or 90% of the drug in the formulation has been taken up by the gut wall before the formulation reaches the large intestine, hence within the approximately 3 to 5 hours after the

formulation has left the stomach. Hence, the composition is such as to prevent release of the sodium cromoglycate from said microgranule/pellet in gastric fluids, but to permit release of the sodium cromoglycate from said microgranule/pellet in intestinal fluids at a rate  
5 allowing treatment of the part of the small intestine, ie at a rate corresponding to a release time of 10 minutes to 10 hours or 1 to 10 hours, preferably 10 minutes to 5 hours or 1 to 5 hours, said rate being measured *in vitro* as a dissolution rate of said unit in simulated gastric and intestinal fluids, when measured in a flow through cell (eg Sotax  
10 Dissotest CE6, equipped with 12 mm cells) at 8 ml/min and 37°C. Typically, (a) not more than 10%, preferably not more than 5%, of the total sodium cromoglycate is released after two hours in simulated gastric fluid (eg USP, pH1.2, without enzymes) in said assembly, (b) from 15 to 55%, preferably from 20 to 50%, of the total sodium cromoglycate is released after two hours in simulated intestinal fluid (eg  
15 USP, pH 7.5, without enzymes) in said assembly, (c) from 35 to 80%, preferably from 40 to 70%, of the total sodium cromoglycate is released after four hours in simulated intestinal fluid in said assembly, (d) not less than 60, preferably 60 to 90%, of the total sodium cromoglycate is released after eight hours in simulated intestinal fluid in said assembly,  
20 (e) not less than 80% of the total sodium cromoglycate is released after ten hours in simulated intestinal fluid in said assembly.

Alternatively, at least 90%, preferably 100% of the total sodium cromoglycate is released within two hours in simulated intestinal fluid  
25 (eg USP, pH 7.5, without enzymes) in said assembly. This may be pH triggered release, not matrix release.



Two particular ways in which the drug can be made bioavailable at differing times, and therefore differing locations of the small intestine as the contents pass through the intestine, are to coat the microgranules/pellets with differing thicknesses of the same enteric coating or to use differing enteric coating materials which dissolve at differing pH's. This may provide a non-pareil formulation. Both formulations take advantage of the fact that the pH of the contents of the intestine gradually rises as the contents pass from the stomach into and through the small intestine. Suitable enteric coatings are known in the art and are discussed in more detail below.

The microgranules/pellets may be taken orally as a suspension in a liquid (for example reconstituted as a suspension in a liquid at the time of use), preferably with food, or they may be packaged in capsules, for example of gelatin, which make the preparation easy to swallow but which disintegrate in the stomach, thus helping to mix the microgranules/pellets evenly with food.

A second aspect of the invention provides a method of treating a patient for an allergic condition by orally administering sodium cromoglycate, characterised in that the patient has first been tested for serum IgE level and has been found to have a total level of at least 150 iu/ml.

Suitable IgE tests include an *in vitro* total IgE test and an *in vitro* specific IgE test, for example the UniCAP Total (or Specific) IgE tests sold by Pharmacia & Upjohn, which use the Allergen ImmunoCAPs as the allergen reagent.

We have found that it is probably necessary, and certainly desirable, for patients to be screened according to their IgE levels before treatment with sodium cromoglycate is undertaken. More specifically, we believe that patients with total serum IgE levels below 150 iu/ml are less likely  
5 to respond to the treatment. Although previous trials have measured IgE levels, the patients have not been selected for treatment according to the IgE level. This is one reason why we believe that the prior art studies have created the impression that sodium cromoglycate is not always effective in treating these allergic conditions.

10

Hence, according to a further aspect of the invention, a patient is selected for therapy according to whether their total serum IgE level is above 150 iu/ml. They may be tested immediately before therapy, or reference may be made to earlier test results.

15

The pathophysiology of food allergy and food allergic disease is unknown but we consider that the primary defect in a number of patients is an allergic inflammatory reaction in the mucosa of small intestine caused by a reaction between specific substances in the food and specific  
20 IgE antibodies to that food produced by the patient. This allergic inflammatory reaction may cause symptoms itself but commonly does not. We consider that it results in an alteration in gut permeability allowing increased absorption of a number of substances, including those substances to which the patient is allergic. It is the increased absorption  
25 of these substances which causes secondary allergic reactions in secondary target organs, such as the skin in the case of atopic dermatitis and urticaria, the bronchial mucosa in the case of asthma, the nasal

mucosa in the case of rhinitis and the colonic mucosa in the case of irritable bowel syndrome.

We further consider that the primary mode of action of orally administered sodium cromoglycate in the treatment of food allergy is to reduce the severity of the IgE-mediated allergic inflammatory reaction in the mucosa of the small intestine and therefore prevent the increased absorption of allergic substances. As the severity of the allergic reaction in the secondary target organs is related to the amount of allergen reaching the organ, this effect of the drug will be to reduce the severity of the allergic reaction in the secondary target organ.

It has recently been shown that an additional effect of sodium cromoglycate is to reduce the ability of IgE-producing cells, the B lymphocytes, to synthesise IgE antibody. It is proposed that the relevant B lymphocytes in the case of food allergy are found in the mucosa of the small intestine.

The present invention therefore provides a long-term treatment with oral sodium cromoglycate, based not only on its ability to reduce the consequences of the acute antigen/IgE antibody reaction but also the overall sensitivity by reducing the local synthesis of IgE antibody. This will initially be seen in the reduction in locally measured IgE antibody and ultimately in the amount of IgE antibody measured systemically, that is in the blood as Total Serum IgE.

The basis of an aspect of this invention is that the efficacy of oral sodium cromoglycate in the treatment of food allergic conditions will be

increased by selecting patients who have clear evidence of an IgE mediated disease and whose clinical response is associated with a reduction in initially local and subsequently systemic levels of IgE antibody and secondly by increasing the bioavailability of the drug with  
5 a formulation that maximises the concentration of the drug in the secretions of the small intestine.

The microgranules/pellets used in the formulation of the present invention may be made by known techniques. Hence, they can be  
10 prepared by coating non-pareil seeds with the sodium cromoglycate or by forming a core comprising sodium cromoglycate dispersed therein. Suitable binding agents which may be used in forming such a core are known in the art. The excipients used to prepare the seeds may comprise one or more of pharmaceutically acceptable materials, eg  
15 sugar, starch, microcrystalline cellulose, waxes and polymeric binding agents, such as those listed below. The first layer on the non-pareil seeds may comprise the sodium cromoglycate and a water-soluble or water-insoluble polymer which acts both as binder for the sodium cromoglycate and as a rate-limiting layer for release of the sodium  
20 cromoglycate. Such polymers may be selected from cellulose derivatives, vinyl polymers and other high molecular polymer derivatives or synthetic polymers such as methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, cellulose acetate, polyvinyl pyrrolidone, polyvidone acetate, polyvinyl  
25 acetate, acrylic polymers and copolymers, polymethacrylates and ethylene-vinyl acetate copolymer or a combination thereof. Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and

methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) in aqueous dispersion form.

5 The optionally first rate-limiting layer on the seeds with homogeneously distributed sodium cromoglycate may comprise a water insoluble polymer or a mixture of water insoluble polymers or a mixture of water soluble and water insoluble polymers mentioned above.

10 The polymers used to coat the core (for example in the absence of a first layer as described above) or used in a second layer may be selected from the group of anionic carboxylic polymers suitable for pharmaceutical purposes and being soluble only with difficulty at a low pH but being soluble at a higher pH, the pH limit for solubility being in the interval of pH 4 to pH 7.5, said group comprising cellulose acetate phthalate,  
15 cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate and acrylic acid polymers eg partly esterified methacrylic acid polymers such as Eudragit L, Eudragit L100-55 and Eudragit S. These polymers may be used alone or in combination with each other or in combination with water insoluble polymers mentioned  
20 before. Preferred polymers are the Eudragits in aqueous dispersion form. The anionic carboxylic polymer may comprise 25 to 100% of the total polymer content.

25 The coatings may optionally comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, anti-adhesives, surfactants, and diffusion-accelerating or diffusion-retarding substances. Suitable plasticizers comprise phthalic acid esters, triacetin, dibutylsebacate, monoglycerides,

citric acid esters and polyethyleneglycols. Preferred plasticizers are acetyltributyl citrate and triethyl citrate. Suitable antiadhesives comprise talc and metal stearates.

- 5 The amount of the first coating applied on the units is normally in the range between 0.5% and 30% by weight, preferably between 1% and 15%. This amount includes in the relevant case the weight of the sodium cromoglycate as well. The amount of the second coating applied on the units is normally in the range between 1% and 50% by weight, 10 preferably between 2% and 25%; calculated on the weight of the coated units. The amount of coating (which may be one or two coatings) applied on the units may be in the range between 1 and 50% or 5% and 60% by weight, preferably between 5% and 50% or 2% to 25%, calculated on the weight of the coated units. The remainder constitutes 15 the weight of the seed or core. It is thus clear that the above percentages refer to the coating as a percentage of the final weight of the units after coating. Alternatively, the amount of the coating may be in the range between 5 and 120%, preferably between 5 and 100%, more preferably between 5 and 50% by weight of the weight of the seed or core or active 20 ingredient.

For example, in one process, sodium cromoglycate powder (in which 90% of the particles may have a diameter of less than 30  $\mu\text{m}$ ) is spray granulated in a fluid bed dryer in combination with water and HPMC to 25 agglomerate the particles into larger particles, which may be cores for coating. The latter are then enteric coated in a fluid bed coater and can then be filled into capsules, compressed into tablets or filled into unit-dose sachets, the contents of which may be suspended in a liquid at a

suitable pH immediately prior to use and drunk by the patient. Alternatively, the sodium cromoglycate can be mixed with a melt binder such as polyethylene glycol, heated to its melting point in a high shear mixer and cooled. This produces rather larger particles of about 200  
5  $\mu\text{m}$ , or 200 to 1100  $\mu\text{m}$ , which are then enteric coated, or packaged and then enteric coated, and presented as the desired oral dosage form as above.

Alternatively, the sodium cromoglycate may be mixed and granulated  
10 with an aqueous binder system in a high shear mixer to produce substantially spherical granules and then dried in a fluid bed drier. Again, larger particles of between 200 and 1100  $\mu\text{m}$  may be produced and then either packaged and enteric coated, or enteric coated.

15 The composition of the coating should be optimised to maximise disintegration of the coating within the small intestine (duodenum, jejunum, ileum) and to minimise the possibility of the coated microgranules/pellets passing through the small intestine, or even the whole gastrointestinal tract, intact. Preferably, drug is made  
20 bioavailable from the duodenum onwards.

Any coating can be used which ensures that the microgranules or capsules do not break up and release the drug until they are in the small intestine. The coating may be one which is pH-sensitive, redox-sensitive  
25 or sensitive to particular enzymes or bacteria, such that the coating only dissolves or finishes dissolving in the small intestine. Thus, the microgranules or capsules will not release the drug until they are in the small intestine.

The amount of the coating will typically be in the range of 4-20% w/w on dry granules, or 5 to 120% w/w of the weight of the dry granules before the coating is applied. The amount of the particular coating used  
5 will be chosen according to the mechanism by which the coating is dissolved. Suitable amounts of coating for a capsule are well known to those skilled in the art.

Preferred coating materials are those which dissolve at a pH of 5 or  
10 above, for example pH 5.5 to 7.5, such as polyacids having a  $pK_a$  of 3 to 5. The coatings therefore only begin to dissolve when they have left the stomach and entered the small intestine. Such a coating can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate  
15 phthalate (PVAP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethyl ethylcellulose (CMEC) and shellac as described by Healy in his article "Enteric Coatings and Delayed Release" Chapter 7 in "Drug Delivery to the Gastrointestinal Tract", editors Hardy *et al*, Ellis Horwood,  
20 Chichester, 1989, or in Chapter 93 of Remington's: "The Science and Practice of Pharmacy", 19th Edition. PVAP is preferred to CAP or CAT, as it dissolves at a lower pH and hence ensures bioavailability from the duodenum onwards.

25 Other materials include methylmethacrylates or copolymers of methacrylic acid and methylmethacrylate. Such materials are available as Eudragit polymers (trademark) (Röhm Pharma, Darmstadt, Germany). Eudragits L, S, "L and S" and LD are anionic copolymers of



methacrylic acid and methylmethacrylate and are generally suitable. For example Eudragit L100 (50% free carboxyl groups) or S100 (30% free carboxy groups) may be used. Eudragit L100-55 is especially suitable and is obtained from L30 D-55 by spray-drying. It has equal amounts of  
5 methacrylic acid and ethyl acrylate and about 50% free carboxyl groups.

The microgranules can also be given a sustained or controlled release property, for example with waxes or silicone elastomers, especially by using melt granulation techniques.

10

A chelator of heavy metal ions, such as EDTA, can be included in the formulation in order to prevent insoluble heavy metal ion salts or complexes of cromoglycate being formed. To be most effective, the chelating agent should be included in the microgranules but,  
15 alternatively, it can be mixed with the microgranules.

Suitable dosage regimes include the following. An initial daily dose of 1 mg to 2 g, preferably 100-1000 mg, more preferably about 200-800 mg, still more preferably about 300 to 500 mg is given in, for example, two  
20 divided doses spaced 12 hours apart. This may be increased at intervals of, say, 1-3 weeks, to a maximum of 1000-5000 mg daily. A typical maximum daily dose is 4000 mg or 100 mg/kg/day (whichever is the greater).

25 Preferred aspects of the invention will now be described by way of reference to non-limiting examples.

### **Example 1**

The following solutions are made up:

Formulation A1, A2 or A3:

5

Formulation A1:

	Water (purified)	1000 g	
10	Sodium Cromoglycate	150 g	)
	Hydroxypropyl methyl cellulose	16.68 g	) solids 14.29%
		<hr/>	)
15		1166.7 g	
		<hr/>	

Formulation A2: (for a larger and stronger granule)

20	Water (purified)	2000 g
	Sodium Cromoglycate	300 g
	Hydroxypropyl methyl cellulose	54 g
25		<hr/>
		2354 g
		<hr/>

30 Formulation A3: (for an even stronger granule)

	Water (purified)	2000 g
	Hydroxypropylmethyl cellulose	222 g
35		<hr/>
		2222 g
		<hr/>

Coating Suspension

Formulation B:		%		<u>for 1000 g of granule</u>
5	Aqoat HPMC-AS-LF	7.0	)	74.55
	Triethyl Citrate	1.96	)	20.87
	Talcum Powder	1.1	) 11.27%	11.72
	Titanium Dioxide	1.0	) solids	10.65
	Sodium Lauryl Sulphate	0.21	)	2.24
10	Purified Water	88.73	)	944.97
		<hr/>		<hr/>
		100.00		1065 g
		<hr/>		<hr/>

15

A 12% coat (solids) on 1000 g of granule at 11.27% solids requires 1065 g of suspension.

1000 g of powder Sodium Cromoglycate is placed into the bowl of an  
20 MPI Spray Granulator (Aeromatic-Fielder-UK) and fluidised using hot  
air at an inlet temperature of 70°C. The air rate used is approx 100  
m<sup>3</sup>/hr.

Once the material is fluidised and the powder bed has reached a  
25 temperature of 40°C, Formulation A1, A2 or A3 is sprayed through a  
two fluid nozzle placed above the fluidised bed, using atomizing air at  
approx 2 bar, to produce granules. The rate used is approx 27 g/min  
and therefore the time taken to spray 1167 g of solution is approx 44  
minutes.

30

Once spraying has been completed the product is allowed to dry in the  
hot air stream until the bed temperature reaches 46°C. (The lowest bed  
temp reached is 35°C.)

If all the powder is collected, then the weight yield should be 1000 + the solution solids = 1166.7 g.

5 However, the typical yields obtained were around 90%.

A choice may be made at this stage between coating the granules individually or filling them into hard gelatin capsules and then coating the capsules.

10

#### Filling into capsules

An appropriate fill of Sodium Cromoglycate, for example 100 or 200 mg per capsule, is weighed into hard gelatin capsules, and the capsules  
15 sealed and enteric coated in a fluidised spray coater or rotary coating pan.

#### Enteric coating the individual granules

20 1000 g of the above produced granules are now transferred to the bowl of a fluid bed coater such as an MPI Precision Coater, which uses an upspray system for spraying a coating solution/suspension on to the fluidised granules.

25 The atomizing air pressure is approx 3 bar.

The bed of granules is preheated to a temperature of approx 36°C (inlet air temperature of 60°C used) before spraying commences.

The coating solution (Formulation B) is sprayed onto the granules at an approx rate of 18 g/min using atomizing air pressure of approx 3 bar and therefore the time taken to spray 1065 g of solution is approx 60 mins (1  
5 hour). During the coating the temperature of the granules gradually drops and by the end has reached approx 25°C. Once all the coat has been added the bed is allowed to heat up to approx 40°C before stopping the process to allow the coat to dry. Total process time including drying is approx 1½ hours (90 mins). In nearly all cases/batches produced to  
10 date the yields have been very good at 100%.

Finally, the coated granules are filled into capsules for the final dosage form.

15 **Example 2**

An alternative method involves the use of high shear mixer technology using a melt granulation technique.

20 Stage one - this process involves mixing SCG with a melt binder such as PEG under ambient conditions. The mixture is then heated to the melt point of the binder (approx 60°C) in a high shear mixer and mixed intensely to produce a round particle of approximate size 200 to 500 µm, and then cooled.

25

Stage two - these particles are then enteric-coated in a fluid bed spray coater (obtainable from Aeromatic-Fielder Ltd, Hampshire, UK) with AQOAT (Shin-Etsu) or one of the other commercially available coatings

such as a CAP (FMC), CAT (Eastman Kodak), PVAP (Colorcon), or a Eudragit (Röhm Pharma).

Stage three - these coated particles may then be used to produce a variety of oral dosage forms such as capsules to be swallowed, or tablets to be swallowed, or filled into unit-dose sachets the contents of which may be suspended in a liquid of suitable pH immediately prior to use and drunk, or partially filled into bottles to which a suitable diluent is added, by the pharmacist immediately prior to it being dispensed, and drunk.

10

### **Example 3**

Patients with symptoms of food allergy or chronic disease such as irritable bowel syndrome, rhinitis, asthma, conjunctivitis, atopic dermatitis, urticaria, migraine, eczema or hyperactivity in which allergy to foods has been shown to be a causative factor are investigated for total serum IgE levels by the Pharmacia & Upjohn UniCAP Total IgE Test, and preferably also investigated for sensitivity to food or drink by the Pharmacia & Upjohn UniCAP Specific IgE Test and/or skin prick tests to ingested allergens. If total serum IgE levels are above 150 iu/ml or if a skin prick test or UniCAP Specific IgE test is positive the patient should be considered for treatment with the formulation of the invention.

Adults and children over 12 years of age should be started on a daily dose of from 400 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules should be swallowed whole with water, not milk, milkshake, fruit juice or other potentially allergic foodstuff.

Children between the ages of 12 and 5 years should be started on a daily dose of from 200 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules should be swallowed as  
5 above.

Children below 5 years of age should be started on a daily dose of from 50 to 100 mg a day taken before food in two divided doses, for example at 8.00 am and 8.00 pm. Capsules should be swallowed as above.

10

Patients may initially experience a worsening of symptoms. This is a positive sign that the medication is having an effect. In these patients the dosage should be reduced to half for 1 week before being increased again. Alternatively an anticholinergic drug such as dicyclomine  
15 hydrochloride or propantheline bromide may be administered concurrently for the first week.

After 4 weeks another serum IgE measurement should be taken. If this is lower it may indicate that the patient is responding even if there is no  
20 symptomatic improvement.

Serum IgE measurements should continue to be taken at monthly intervals for 6 months, 3 monthly for a further 6 months and 6 monthly thereafter. A maintained reduction in levels will indicate a reduction in  
25 sensitivity to the ingested allergens and symptomatic improvement in the condition.

It is important that patients continue to take their medication even though their symptoms are absent or significantly improved. If they do not, their IgE levels will begin to increase again and when they start the medication again it will take time for the IgE levels and therefore the  
5 symptoms to subside - but patients will not wait and will conclude that the medication is ineffective.



**CLAIMS**

1. An oral drug delivery composition comprising a chromone,  
characterised in that the chromone is made bioavailable in the  
small intestine following human oral administration.
2. A composition according to Claim 1 wherein the composition  
comprises microgranules of up to 1.5 mm diameter which are  
contained in a hard or soft capsule, which capsule has an enteric  
coating.
3. A composition according to Claim 2 wherein the capsule consists  
essentially of gelatin.
4. A composition according to any one of Claims 1 to 3 wherein the  
composition comprises microgranules of up to 1.5 mm diameter,  
each microgranule having an enteric coating.
5. A composition according to any one of Claims 2 to 4 wherein the  
size of the microgranules is 25-250  $\mu\text{m}$  or 200 to 1100 $\mu\text{m}$ .
6. A composition according to Claim 5 wherein the size of the  
microgranules is 50-100  $\mu\text{m}$ .
7. A composition according to any one of Claims 4 to 6 wherein said  
microgranules do not all have the same enteric coating, such that  
the content of the microgranules is made bioavailable at differing  
locations in the small intestine.

8. A composition according to Claim 7 wherein the thickness of the coating is not the same for each microgranule.
- 5 9. A composition according to Claim 7 or 8 wherein the coating material is varied.
10. A composition according to any one of Claims 4 to 9 wherein the microgranules are packaged in one or more capsules formed of a  
10 material which will release the microgranules in the stomach.
11. A composition according to any one of the preceding claims additionally comprising a chelator of heavy metal ions, such as EDTA.  
15
12. A composition according to any one of the preceding claims wherein the chromone is sodium cromoglycate.
13. A method of treating a patient for an allergic condition  
20 comprising administering to the patient a composition according to any one of the preceding claims.
14. A method according to Claim 13 wherein a daily dose of 100-5000 mg is delivered.
- 25 15. A method of treating a patient for an allergic condition by orally administering a chromone, characterised in that the patient has

first been selected to have a total serum IgE level of at least 150 iu/ml.

- 5 16. A method according to Claim 15 wherein the serum IgE level of the patient is tested during the course of the treatment and the dose of chromone is increased or prolonged if the level has not fallen to, or is not falling towards, 150 iu/ml.
- 10 17. A method according to any one of Claims 13 to 16 wherein the patient is also given anti-muscarinic medication so that at least part of the effect of the chromone treatment overlaps temporally with at least part of the effect of the anti-muscarinic treatment.
- 15 18. The use of a chromone in the preparation of a medicament for the treatment of an allergic condition in a patient selected on the basis of having a total serum IgE level of at least 150 iu/ml.

## INTERNATIONAL SEARCH REPORT

International Application No  
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IPC 6 A61K31/35 A61K9/16

According to International Patent Classification(IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 85 00015 A (PHARMACIA AB) 3 January 1985 *cf. abstract, page 6, 3rd para, page 7, 3rd para., page 12, last para. bridging with page 13, 1st para., page 17, last para., claim 1* ---	1-18
X	GB 1 423 985 A (FISONS LTD) 4 February 1976 cited in the application *cf. left col. on page 1, lines 24-35, right col. on page 1, last para. bridging with page 2, left col. 1st para..* --- -/--	1-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 1 549 229 A (FISONS LTD) 1 August 1979 cited in the application *cf. page 1, left col., lines 9-17, right col., last para., example 1 on page 2 bridging with page 3, first para. on the left col..*	1-18
Y	GB 1 569 612 A (FISONS LTD) 18 June 1980 *cf. page 1, left col., lines 33-48 and right col., first para. and last para. bridging with left col. of page 2, lines 1-4*	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01353

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8500015 A	03-01-1985	AU 3068784 A	11-01-1985
		CA 1226219 A	01-09-1987
		DK 69685 A,B,	14-02-1985
		EP 0130163 A	02-01-1985
		EP 0145778 A	26-06-1985
		FI 850619 A,B,	14-02-1985
		JP 60501559 T	19-09-1985
		US 4642232 A	10-02-1987
GB 1423985 A	04-02-1976	US 4421762 A	20-12-1983
		US 4152448 A	01-05-1979
GB 1549229 A	01-08-1979	AU 508134 B	13-03-1980
		AU 2898377 A	29-03-1979
		DE 2741202 A	30-03-1978
		FR 2365565 A	21-04-1978
		JP 1037369 B	07-08-1989
		JP 1562296 C	12-06-1990
		JP 53040776 A	13-04-1978
		NL 7710382 A,B,	29-03-1978
		ZA 7705625 A	26-07-1978
GB 1569612 A	18-06-1980	NONE	